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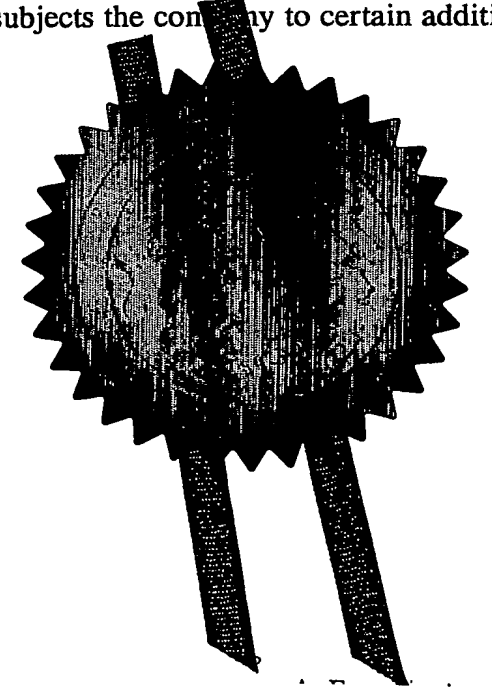

Signed Andrew Guy

Dated 16 January 2004

Patents Form 1/77

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1/77

Request for grant of a patent

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1.	Your reference	**4-33144P1**
2.	Patent application number *(The Patent Office will fill in this pa*	0307855.7
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**NOVARTIS AG** **LICHTSTRASSE 35** **4056 BASEL** **SWITZERLAND**
	Patent ADP number *(if you know it)*	7125487005
	If the applicant is a corporate body, give the country/state of its incorporation	**SWITZERLAND**
4.	Title of invention	**Organic Compounds**
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**B.A. YORKE & CO.** **CHARTERED PATENT AGENTS** **COOMB HOUSE, 7 ST. JOHN'S ROAD** **ISLEWORTH** **MIDDLESEX TW7 6NH**
	Patents ADP number *(if you know it)*	**1800001**

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*	**Yes**
	a) any applicant named in part 3 is not an inventor, or	
	b) there is an inventor who is not named as an applicant, or	
	c) any named applicant is a corporate body.	
	(see note (d))	

04 APR 2003

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Continuation sheets of this form	
Description	14
Claim(s)	3
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B.A. Yorke & Co. Date: 4th April 2003

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom: **Mrs. S. Schnerr** **020 8560 5847**

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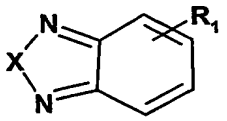
DUPLICATE

Organic Compounds

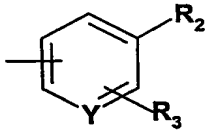
The present invention relates to novel benzo[1,2,5]oxadiazoles and benzo[1,2,5]thiadiazoles, their preparation, their use as markers and compositions containing them.

More particularly the invention provides a compound of formula I



I

wherein X is O or S, R_1 is 5-(2-fluoro-ethylamino)-thiazol-2-yl, 5-(2-^{18}F-ethylamino)-thiazol-2-yl or a group of formula (a)

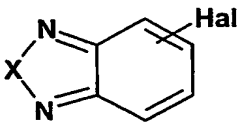


(a)

wherein Y is CH or N, R_2 is $NHCH_3$, $NH^{11}CH_3$, $N(CH_3)^{11}CH_3$, $N(CH_3)_2$, $N(^{11}CH_3)_2$, $NH(CH_2)_nF$, $NH(CH_2)_n{}^{18}F$, $N(CH_3)$-$(CH_2)_nF$, $N(CH_3)$-$(CH_2)_n{}^{18}F$, O-$(CH_2)_nF$, O-$(CH_2)_n{}^{18}F$, $CONH(CH_2)_nF$ or $CONH(CH_2)_n{}^{18}F$ (n being in each case 2 to 4) and R_3 is hydrogen or nitro, in free base or acid addition salt form.

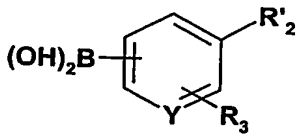
In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, comprising the steps of

a) for the production of a compound of formula I which contains no ^{11}C or ^{18}F atom, reacting a compound of formula II



II

wherein X is as defined above and Hal is Cl, Br or I, with 5-(2-fluoro-ethylamino)thiazolyl-2-boronic acid or a compound of formula III



III

wherein Y and R_3 are as defined above and R'_2 is a group R_2 as defined above which contains no ^{11}C or ^{18}F atom, or

b) for the production of a compound of formula I wherein R_1 is 5-(2-^{18}F-ethylamino)-thiazol-2-yl, reacting a compound of formula I wherein R_1 is 5-(2-mesyloxy-ethylamino)-thiazol-2-yl or 5-(2-tosyloxy-ethylamino)-thiazol-2-yl with $^{18}F^{\ominus}$, or

c) for the production of a compound of formula I wherein R_2 is $NH^{11}CH_3$, $N(CH_3)^{11}CH_3$ or $N(^{11}CH_3)_2$, reacting a compound of formula I wherein R_2 is NH_2 or $NHCH_3$ with $^{11}CH_3I$, or

d) for the production of a compound of formula I wherein R_2 is $NH(CH_2)_n{}^{18}F$, $N(CH_3)$-$(CH_2)_n{}^{18}F$, O-$(CH_2)_n{}^{18}F$ or $CONH(CH_2)_n{}^{18}F$, reacting a compound of formula I wherein R_2 is, respectively, $NH(CH_2)_nOTs$ or $NH(CH_2)_nOMs$, $N(CH_3)$-$(CH_2)_nOTs$ or $N(CH_3)$-$(CH_2)_n$-OMs, O-$(CH_2)_nOTs$ or O-$(CH_2)_n$-OMs, or $CONH(CH_2)_nOTs$ or $CONH(CH_2)_nOMs$, with $^{18}F^{\ominus}$,

and recovering the resulting compound of formula I in free base form or in form of an acid addition salt.

The reaction described under a) can be effected according to known methods, for example as described in Example 1.

Alternatively to process a), conventional methods can be used for the production of compounds of formula I which contain no ^{11}C or ^{18}F atom, for example as described in Examples 7 and 13 to 19.

The reactions described under b), c) and d) can be effected according to conventional methods.

Working up the reaction mixtures and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced from the free bases in known manner, and vice-versa.

Compounds of formula I in free base or acid addition salt form, hereinafter referred to as agents of the invention, exhibit valuable properties as histopathological staining agents, imaging agents and/or biomarkers, hereinafter "markers".

More particularly the agents of the invention are useful as markers for labeling pathological structures such as extracellular ß-amyloid deposits, e.g. in the brain of patients with Alzheimer's disease (see Example ?).

The agents of the invention are therefore useful for the early diagnosis and prevention of Alzheimer's disease and for monitoring the effectiveness of therapeutic treatments of Alzheimer's disease.

The advantages of assessing amyloid deposits in vivo and non-invasively using markers capable of labeling these structures have been reported e.g. in WO 00/10614.

In accordance with the above, the present invention provides a composition for labeling histopathological structures in vivo or in vitro, comprising an agent of the invention.

In a further aspect, the present invention provides a method for labeling histopathological structures in vitro or in vivo, which comprises contacting brain tissue with an agent of the invention.

Said brain tissue comprises for example ß-amyloid deposit.

Contacting the brain tissue with the agent of the invention is for example effected by administering the agent of the invention to a patient, e.g. a patient with Alzheimer's disease.

The method of the invention may comprise a further step aimed at determining whether the agent of the invention labeled the target structure.

If the agent of the invention is a non-radioactive compound of formula I, said further step may be effected by observing the target structure using fluorescence microscopy.

If the agent of the invention is a radioactive compound of formula I, said further step may be effected by observing the target structure using positron emission tomography (PET).

Labeling histopathological structures in vitro is effected, for example, for detecting histopathological hallmarks of Alzheimer's disease.

Labeling histopathological structures in vivo is effected, for example, for diagnosing Alzheimer's disease in a patient or for monitoring the effectiveness of a therapeutic treatment of Alzheimer's disease.

The following examples illustrate the invention.

Example 1: (4-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-dimethyl-amine

500 mg (2.5 mmol) 5-bromo-benzo[1,2,5]oxadiazole and 313 mg (0.1 eq.) tetrakis(triphenylphosphine)palladium are stirred for 30 minutes at room temperature in 10 mL 1,2-dimethoxyethane. 533 mg (2 eq.) sodium carbonate are dissolved in 1.8 mL water and added to the reaction mixture, followed by 663 mg (1.6 eq.) 4-(dimethylamino)phenylboronic acid. After stirring at reflux for 18h, the reaction mixture is cooled to room temperature and extracted with ethyl acetate and water. The organic phases are combined, dried with magnesium sulfate, filtered and evaporated. The residue is column chromatographed (hexane, then hexane/ethyl acetate 8:1 then 5:1) to yield 170 mg (28%) desired product as a yellow solid. MS(ES+): 240 (M+1).

^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 7.83 (d, H_{arom}); 7.82 (s, H_{arom}); 7.73 (d, H_{arom}); 7.58, 6.81 (2d, 2x2H_{arom}); 3.05 (s, 2Me).

The following compounds of examples 2 to 6 can be prepared according to the same procedure:

Example 2: (4-Benzo[1,2,5]thiadiazol-4-yl-phenyl)-dimethyl-amine

Starting from 4-iodo-benzo[1,2,5]thiadiazole and 4-(dimethylamino)phenylboronic acid. Orange powder. MS(ES+): 256 (M+1)

Example 3: (4-Benzo[1,2,5]oxadiazol-4-yl-phenyl)-dimethyl-amine

Starting from 4-chloro-benzo[1,2,5]oxadiazole and 4-(dimethylamino)phenylboronic acid. Orange powder.MS(ES+): 240 (M+1).

Example 4: (3-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-methyl-amine

Starting from 5- benzo[1,2,5]oxadiazoleboronic acid and (3-bromo-phenyl)-methyl-amine. Yellow powder. MS(ES+): 226 (M+1)

Example 5: 5-[4-(2-Fluoro-ethoxy)-phenyl]-benzo[1,2,5]oxadiazole

Starting from 5-benzo[1,2,5]oxadiazoleboronic acid and 1-bromo-4-(2-fluoro-ethoxy)-benzene. Yellow-beige powder. MS(ES+): 259 (M+1)

Example 6: (3-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-dimethyl-amine

Starting from 5- benzo[1,2,5]oxadiazoleboronic acid and (3-bromo-phenyl)-dimethyl-amine. Orange-yellow powder. MS(ES+): 240 (M+1)

Example 7: (2-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-dimethyl-amine

523 mg (1.65 eq.) Bis(pinacolato)diboran, 552 mg (4.5 eq.) potassium acetate and 51 mg (0.01 eq.) PdCl(dppf)-CH_2Cl_2 are added to a solution of 373 mg 5-bromo-benzo[1,2,5]oxadiazole in 8 mL DMF and heated to 80°C under continuous stirring for 6 hours. 662 mg (5 eq) sodium carbonate in 3.3 mL water are added together with 500 mg (1 eq.) 2-bromo-N,N-dimethylaniline and 51 mg (0.01 eq.) PdCl(dppf)-CH_2Cl_2 to the reaction mixture, which is stirred for another 18 hours at 80°C, cooled to room temperature and extracted with ethyl acetate and water. The combined organic phases are washed with brine, dried over magnesium sulfate and evaporated. The residue is column chromatographed (hexane, then hexane/ethyl acetate 8:1) to yield 185 mg (62%) desired product as an orange resin. MS(ES+): 240 (M+1).

^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 7.77 (s, H_{arom}); 7.71, 7.69 (2d, $2H_{arom}$); 7.25, 7.03 (2m, $2x2H_{arom}$); 2.53 (s, 2Me).

The following compounds of Examples 8 to 12 are synthesized according to the same procedure:

Example 8: (2-Benzo[1,2,5]thiadiazol-5-yl-phenyl)-dimethyl-amine

Starting from 5-bromo-benzo[1,2,5]thiadiazole and 2-bromo-N,N-dimethylaniline. Orange resin. MS(ES+): 256 (M+1).

Example 9: (3-Benzo[1,2,5]oxadiazol-4-yl-phenyl)-methyl-amine.

Starting from 5-chloro-benzo[1,2,5]oxadiazole and (3-bromo-phenyl)-methyl-amine. Yellow powder. MS(ES+): 226 (M+1).

The starting material is obtained as follows:

(3-Bromo-phenyl)-methyl-amine

2g (11.6 mmol) 3-Bromoaniline is dissolved in 15 mL DMF and treated with 716 mg (1.1 eq.) KOH and 0.722 mL (1 eq.) iodomethane under continuous stirring at room temperature for 20 hours. The reaction mixture is extracted with ethyl acetate and water, the combined organic phases are washed with brine and dried with sodium sulfate and evaporated to dryness. The residue is column chromatographed (ethyl acetate/petroleum ether 2:5) to yield after evaporation 980 mg (45%) desired product as a yellow oil.

Example 10: 4-[4-(2-Fluoro-ethoxy)-phenyl]-benzo[1,2,5]oxadiazole.

starting from 4-chloro-benzo[1,2,5]oxadiazole and 1-bromo-4-(2-fluoro-ethoxy)-benzene. Yellow crystals. MS(ES+): 259 (M+1).

Example 11: 5-Benzo[1,2,5]oxadiazol-5-yl-N-(2-fluoro-ethyl)-nicotinamide

Starting from 5-bromo-benzo[1,2,5]oxadiazole and 5-bromo-N-(2-fluoro-ethyl)-nicotinamide. Beige powder. MS(ES-). 285 (M-1).

The starting material is obtained as follows:

5-Bromo-N-(2-fluoro-ethyl)-nicotinamide

2.03 g (10 mmol) 5-Bromonicotinic acid, 1 g (1 eq.) 2-fluoroethylamine, 2.31 g (1.2 eq.) EDC.HCl, 123 mg (0.1 eq.) DMAP and 5.6 mL (4 eq.) triethylamine are stirred in 60 mL dichloromethane for 20 hours at room temperature. The reaction mixture is extracted with dichloromethane and water, the combined organic phases are washed with brine, dried with sodium sulfate and evaporated. The residue is triturated in diethylether and hexane to yield after filtration 970 mg desired product as a white powder. MS(ES+): 347 and 349 (M+1).

Example 12: 4-Benzo[1,2,5]oxadiazol-5-yl-N-(2-fluoro-ethyl)-nicotinamide.

Starting from 4-chloro-benzo[1,2,5]oxadiazole and 5-bromo-N-(2-fluoro-ethyl)-nicotinamide. Beige powder. MS(ES-): 285 (M-1).

Example 13: (4-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-methyl-amine

510 mg (1.57 eq.) (4-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-methyl-carbamic acid tert-butyl ester are dissolved in 10 mL dichloromethane, treated with 0.126 mL (1.05 eq.) trifluoroacetic acid and stirred overnight at room temperature. The reaction mixture is evaporated and the residue column chromatographed (hexane, hexane/ethyl acetate 4:1 then 3:1) to yield 45 mg (13%) desired product as an orange solid. MS(ES+): 226 (M+1).

^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 7.82 (d, H_{arom}); 7.81 (s, H_{arom}), 7.71 (d, H_{arom}); 7.54, 6.72 (2d, 2x2H_{arom}); 2.92 (s, Me).

The starting material is obtained according to the procedure described in Example 7 from 5-bromo-benzo[1,2,5]oxadiazole and (4-bromo-phenyl)-methyl-carbamic acid tert-butyl ester, as a yellow powder.

^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 7.84 (s, H_{arom}); 7.82, 7.63 (2d, 2H_{arom}); 7.54, 7.18 (2d, 2x2 H_{arom}); 3.26 (s, Me); 1.43 (s, tBu).

The following compound is prepared according to the same procedure:

Example 14: (4-Benzo[1,2,5]thiadiazol-5-yl-phenyl)-methyl-amine.

Starting from (4-benzo[1,2,5]thiadiazol-5-yl-phenyl)-methyl-carbamic acid tert-butyl ester. MS(ES+): 242 (M+1).

The starting compound is obtained according to the procedure described in Example 7 from 5-bromo-benzo[1,2,5]thiadiazole and (4-bromo-phenyl)-methyl-carbamic acid tert-butyl ester, as a yellow powder.

^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 8.08 (s, H_{arom}); 7.98, 7.80 (2d, $2H_{arom}$); 7.60, 7.33 (2d, 2x2 H_{arom}); 3.26 (s, Me); 1.43 (s, tBu).

The starting material is obtained as follows:

a) (4-Bromo-phenyl)-methyl-carbamic acid tert-butyl ester

0.263 mL (1.1 eq.) Iodomethane are added dropwise at room temperature to a stirred suspension of 1.1 g (4 mmol) (4-bromo-phenyl)-carbamic acid tert-butyl ester and 2 g (1.6 eq.) cesium carbonate in 15 mL DMF. After stirring for an additional18 hours, the reaction mixture is extracted with water/ethyl acetate and the combined organic phases are washed with brine, dried over magnesium sulfate and evaporated to yield 1.12 g (97%) desired product as a colourless oil, which is used without further purification.

b) (4-Bromo-phenyl)-carbamic acid tert-butyl ester

2 mL (1.2 eq.) Triethylamine are added to a solution of 2g (11.6 mmol) p-bromo-aniline in 25 mL THF. The reaction mixture is cooled to 0°C and treated with 2.66 g (1.05 eq.) Boc_2O under continuous stirring, then allowed to reach 20°C, stirred for an additional 20 hours and extracted with water/ethyl acetate. The combined organic phases are washed with brine, dried over magnesium sulfate and evaporated. The residue is column chromatographed (hexane, hexane/ethyl acetate 7:1 then 4:1) to yield after evaporation and recrystallization from hexane 1.1 g (33%) desired product as a white powder.

Example 15: (4-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-(2-fluoro-ethyl)-methyl-amine

220 mg (0.98 mmol) (4-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-methyl-amine are dissolved in 5 mL DMF, treated with 1.9 g (6 eq.) cesium carbonate, 320 mg (2 eq.) potassium iodide and 0.364 mL (5 eq.) 1-bromo-2-fluoroethane, and stirred for 20 hours at 50°C. The reaction mixture is extracted with water and ethyl acetate, the combined organic phases are washed with water and brine, dried over magnesium sulfate and evaporated. The residue is column chromatographed (gradient from hexane to ethyl acetate) to yield the desired product as an orange powder.

^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 7.77 (d, H_{arom}); 7.75 (s, H_{arom}), 7.65 (d, H_{arom}); 7.51, 6.75 (2d, 2x2H_{arom}); 4.57, 3.67 (2m, $2CH_2$); 3.04 (s, Me).

Example 16: (4-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-methyl-amine

600 mg (2.83 mmol) 3-benzo[1,2,5]oxadiazol-5-yl-phenol are dissolved in 15 mL DMF and stirred for 20 hours at room temperature in the presence of 1.15 g (1.25 eq.) cesium carbonate and 0.264 mL 1-bromo-2-fluoroethane. The reaction mixture is extracted with water and ethyl acetate, the combined organic phases are washed with water and brine, dried with magnesium sulfate and evaporated to dryness. The residue is column chromatographed (gradient from hexane to hexane/ethyl acetate 3:2) to yield the desired product as a pale yellow powder. MS(ES+): 259 (M+1).

^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 7.95 (s, H_{arom}), 7.90 (d, H_{arom}); 7.70 (d, H_{arom}); 7.42 (m, H_{arom}); 7.27 (m, H_{arom}); 7.22 (s, H_{arom}); 7.04 (m, H_{arom}); 4.80, 4.31 (2m, $2CH_2$).

The starting material 3-Benzo[1,2,5]oxadiazol-5-yl-phenol is obtained according to the procedure described in Example 1 starting from 5-bromo-benzo[1,2,5]oxadiazole and 3-hydroxyphenylboronic acid, as a light yellow powder.

^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 7.94 (s, H_{arom}); 7.92, 7.68 (2d, 2 H_{arom}); 7.38 (t, H_{arom}); 7.24 (d, H_{arom}); 7.13 (s, H_{arom}); 6.94 (d, H_{arom}); 4.93 (OH).

Example 17: (2-Benzo[1,2,5]oxadiazol-5-yl-thiazol-5-yl)-(2-fluoro-ethyl)-amine

53 mg (0.2 mmol) Benzo[1,2,5]oxadiazole-5-carboxylic acid [(2-fluoro-ethylcarbamoyl)-methyl]-amide and 97 mg (1.2 eq.) Lawesson's reagent are suspended in 20 mL toluene and heated to reflux for one hour. After cooling to room temperature, the reaction mixture is poured onto ice-water containing 2 mL of a saturated aqueous solution of sodium carbonate, then extracted with ethyl acetate. The combined organic phases are dried with sodium sulfate and evaporated to dryness. The residue is column chromatographed (petroleum ether/ethyl acetate 3:2) to yield after evaporation of the corresponding fractions 21 mg (39%) desired product as an orange powder. MS (ES+): 265 (M+1).

^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 8.12 (d, H_{arom}), 7.95 (s, H_{arom}); 7.82 (d, H_{arom}); 7.04 (s, H_{het}); 4.70, 3.53 (2m, $2CH_2$).

The starting materials were obtained as follows:

a) Benzo[1,2,5]oxadiazole-5-carboxylic acid [(2-fluoro-ethylcarbamoyl)-methyl]-amide
221 mg (1 mmol) [(Benzo[1,2,5]oxadiazole-5-carbonyl)-amino]-acetic acid, 120 mg (1.2 eq.) 2-fluoroethylamine, 162 mg (1.2 eq.) HOBT and 230 mg (1.2 eq.) EDC.HCl are dissolved in 18 mL DMF and cooled to 5°C. 0.7 mL (4 eq.) Hünig's base are added under stirring, the reaction mixture is stirred for an additional 3 hours at room temperature then extracted with water and ethyl acetate. The combined organic phases are washed with brine, dried with sodium sulfate and evaporated to yield 120 mg (45%) desired product as a beige solid.
MS (ES+): 267 (M+1).

b) [(Benzo[1,2,5]oxadiazole-5-carbonyl)-amino]-acetic acid
500 mg (2.13 mmol) [(Benzo[1,2,5]oxadiazole-5-carbonyl)-amino]-acetic acid methyl ester are treated in 50 mL methanol with 6 mL (3 eq.) 1N KOH in methanol containing 10% water at room temperature for two hours, then cooled below 5°C and neutralized with 6 mL 1N aqueous HCl. The reaction mixture is extracted with ethyl acetate, the combined organic phases are washed with brine and dried with sodium sulfate, then evaporated to dryness to yield 450 mg (95%) desired product as a beige-pinkish powder. MS (ES-): 220 (M-1)

c) [(Benzo[1,2,5]oxadiazole-5-carbonyl)-amino]-acetic acid methyl ester
492 mg (3 mmol) Benzo[1,2,5]oxadiazole-5-carboxylic acid 376 mg (1 eq) glycine methyl ester hydrochloride, 486 mg (1.2 eq.) HOBT and 690 mg (1.2 eq.) EDC.HCl are dissolved in 20 mL DMF under argon and the reaction mixture is stirred at room temperature for 90 minutes after addition of 2 mL (4 eq.) Hünig's base. The reaction mixture is poured onto ice and brine, and extracted with ethyl acetate. The combined organic phases are dried with sodium sulfate and evaporated to yield 500 mg (71%) desired product as a beige powder.
MS (ES+): 236 (M+1).

Example18: (4-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-(2-fluoro-ethyl)-amine

391 mg (1 mmol) (4-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-(2-fluoro-ethyl)-carbamic acid benzyl ester are hydrogenated in the presence of Pd/C, the reaction mixture filtered through celite and evaporated to dryness. The residues is column chromatographed (dichloromethane/ petroleum ether 8:2) to yield the desired product as a yellow powder. MS(ES+): 258 (M+1). ^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 7.82 (d, H_{arom}), 7.81 (s, H_{arom}); 7.70 (d, H_{arom}); 7.53 (m, $2H_{arom}$); 6.75 (m, $2H_{arom}$); 4.66, 3.51 (2m, $2CH_2$).

The starting material is obtained according to the procedure described in Example 1 from 5-benzo[1,2,5]oxadiazoleboronic acid and (4-bromo-phenyl)-(2-fluoro-ethyl)-carbamic acid benzyl ester, as a light brown resin. MS(ES+): 392 (M+1).

The starting compound can be synthesized as follows:

a) (4-bromo-phenyl)-(2-fluoro-ethyl)-carbamic acid benzyl ester
2.9g (6 mmol) Phenyl-methanesulfonic acid 2-[benzyloxycarbonyl-(4-bromo-phenyl)-amino]-ethyl ester are dissolved in 100 mL THF and stirred for 18 hours at room temperature after addition of a 1M solution of tetrabutyl-ammonium fluoride in THF. The reaction mixture is poured onto ice and extracted with tertbutyl-methyl ether and a saturated aqueous solution of sodium bicarbonate. The combined organic phases are washed with brine, dried with sodium sulfate and evaporated to dryness. The crude product is column chromatographed (petroleum ether/ethyl acetate 4:1) to yield 920 mg desired product as a yellow resin (44% from 2-(4-bromo-phenylamino)-ethanol). MS(ES+): 352 (M+1).

b) Phenyl-methanesulfonic acid 2-[benzyloxycarbonyl-(4-bromo-phenyl)-amino]-ethyl ester
1.3 g (6 mmol) 2-(4-Bromo-phenylamino)-ethanol are dissolved in 150 mL toluene, treated with 0.93 mL (1.1 eq.) benzyloxycarbonylchloride and 6.3 mL (1.05 eq.) 1N aqueous sodium hydroxide solution. The reaction mixture is stirred at room temperature for 18 hours, then the aqueous phase separated and extracted with ethyl acetate and water. The combined organic phases are washed with water and brine, then evaporated to dryness to yield 2.1 g crude (4-bromo-phenyl)-(2-hydroxy-ethyl)-carbamic acid benzyl ester, which is reacted further without additional purification by dissolution in 100 mL dichloromethane, addition of 5 mL (excess) pyridine, cooling to 5°C and dropwise addition in 10 minutes of 2.45 g *p*-toluenesulfonic acid

anhydride in 20 mL dichloromethane. The reaction mixture is stirred an additional 2 hours at room temperature and poured onto ice, then extracted at 10°C with dichloromethane and an aqueous solution of sodium bicarbonate. The combined organic phases are dried with sodium sulfate and evaporated to yield 2.9g desired product as a light brownish resin, which is used without further purification.

Example 19: (4-Benzo[1,2,5]oxadiazol-5-yl-2-nitro-phenyl)-methyl-amine

140 mg (0.62 mmol) (4-Benzo[1,2,5]oxadiazol-5-yl-phenyl)-methyl-amine are stirred at 0°C in 2 mL concentrated sulfuric acid, then treated with 66 mg (1.05 eq.) potassium nitrate and stirred an additional 4 hours. The reaction mixture is poured onto ice, the precipitate filtered off, thoroughly washed with water and dried under high vacuum. The crude product is column chromatographed with ethyl acetate/petroleum ether 1:2 to yield after evaporation of the product-containing fraction 60 mg (36%) desired product as an orange solid.
MS(ES-): 269 (M-1).

^{1}H-NMR ($CDCl_3$, 400 MHz): delta (ppm) = 8.55 (s, H_{arom}); 8.22 (br.s, NH); 7.92 (d, H_{arom}), 7.91 (s, H_{arom}); 7.82 (d, H_{arom}); 7.72 (d, H_{arom}); 7.01 (d, H_{arom}); 3.13 (s, Me).

Example 20:

Staining of APP23 mouse and human Alzheimer disease (AD) brain sections using an agent of the invention or Thioflavine S.

Four-micrometer thick paraffin sections from an APP23 mouse at 26 months of age are deparaffinized in xylene and rehydrated. 10 mg of the compound are dissolved in 1 ml DMSO and diluted with deionized water 1:10. This staining solution is applied on sections for about 20 min. Section background is cleared by washing with 95% ethanol. Finally sections are dehydrated in 99% ethanol, cleared in xylene and mounted with Vectashield ^{tm}. Sections are investigated using fluorescence microscopy with the following filter combination: Excitation 450-490 nm, emission 510 nm. Twenty micrometer thick cryotom sections from a AD brain cortex are air dried and fixated in 4% PFA for 5 min. After washing in tap water sections are stained either with Thioflavine S or with the compound for 5 min and further

processed as described above. The compound is dissolved in DMSO and diluted to a final concentration of 0.01 % with 50% Ethanol, Thioflavine S is dissolved in 50% Ethanol, final concentration is 0.01 %.

Results:

(These results do not apply to the compounds of Examples 4, 5, 11, 12 and 19, which are not fluorescent)

1) Staining of APP23 mice brain sections

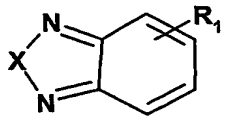
The agents of the invention strongly stain amyloid deposits and vascular deposits in brain sections of APP23 mice.

2) Staining of human AD brain sections:

Brain sections taken from frontal cortex of AD patients are stained with the agents of the invention, and the results compared with a Thioflavine S stain. The agents of the invention intensely and selectively stain amyloid deposits.

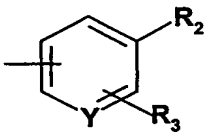
Claims

1. A compound of formula I



I

wherein X is O or S, R_1 is 5-(2-fluoro-ethylamino)-thiazol-2-yl, 5-(2-^{18}F-ethylamino)-thiazol-2-yl or a group of formula (a)

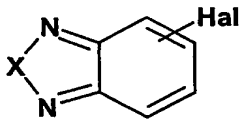


(a)

wherein Y is CH or N, R_2 is $NHCH_3$, $NH^{11}CH_3$, $N(CH_3)^{11}CH_3$, $N(CH_3)_2$, $N(^{11}CH_3)_2$, $NH(CH_2)_nF$, $NH(CH_2)_n{}^{18}F$, $N(CH_3)$-$(CH_2)_nF$, $N(CH_3)$-$(CH_2)_n{}^{18}F$, O-$(CH_2)_nF$, O-$(CH_2)_n{}^{18}F$, $CONH(CH_2)_nF$ or $CONH(CH_2)_n{}^{18}F$ (n being in each case 2 to 4) and R_3 is hydrogen or nitro, in free base or acid addition salt form.

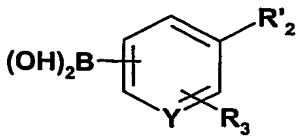
2. A process for the production of a compound of formula I as defined in claim 1 and its salts, comprising the steps of

a) for the production of a compound of formula I which contains no ^{11}C or ^{18}F atom, reacting a compound of formula II



II

wherein X is as defined in claim 1 and Hal is Cl, Br or I, with 5-(2-fluoro-ethylamino)thiazolyl-2-boronic acid or a compound of formula III



III

wherein Y and R_3 are as defined above and R'_2 is a group R_2 as defined above which contains no ^{11}C or ^{18}F atom, or

b) for the production of a compound of formula I wherein R_1 is 5-(2-^{18}F-ethylamino)-thiazol-2-yl, reacting a compound of formula I wherein R_1 is 5-(2-mesyloxy-ethylamino)-thiazol-2-yl or 5-(2-tosyloxy-ethylamino)-thiazol-2-yl with $^{18}F^{\ominus}$, or

c) for the production of a compound of formula I wherein R_2 is $NH^{11}CH_3$, $N(CH_3)^{11}CH_3$ or $N(^{11}CH_3)_2$, reacting a compound of formula I wherein R_2 is NH_2 or $NHCH_3$ with $^{11}CH_3I$, or

d) for the production of a compound of formula I wherein R_2 is $NH(CH_2)_n{}^{18}F$, $N(CH_3)$-$(CH_2)_n{}^{18}F$, O-$(CH_2)_n{}^{18}F$ or $CONH(CH_2)_n{}^{18}F$, reacting a compound of formula I wherein R_2 is, respectively, $NH(CH_2)_nOTs$ or $NH(CH_2)_nOMs$, $N(CH_3)$-$(CH_2)_nOTs$ or $N(CH_3)$-$(CH_2)_n$-OMs, O-$(CH_2)_nOTs$ or O-$(CH_2)_n$-OMs, or $CONH(CH_2)_nOTs$ or $ONH(CH_2)_nOMs$, with $^{18}F^{\ominus}$,

and recovering the resulting compound of formula I in free base form or in form of an acid addition salt.

3. A composition for labeling histopathological structures in vitro or in vivo, comprising a compound of formula I as defined in claim 1, in free base or acid addition salt form.

4. A method for labeling histopathological structures in vitro or in vivo, comprising contacting brain tissue with a compound of formula I as defined in claim 1, in free base or acid addition salt form.

5. A method according to claim 4, for labeling ß-amyloid deposits.

6. A method according to claim 4 or 5, comprising administering the compound of formula I to a patient.

7. A method according to any of claims 4 to 6, comprising the further step of determining whether the compound of formula I labeled the target structure.

8. A method according to claim 7, comprising observing the target structure labeled with a non-radioactive compound of formula I, using fluorescence microscopy.

9. A method according to claim 7, comprising observing the target structure labeled with a radioactive compound of formula I, using positron emission tomography (PET).

10. A method according to any one of claims 4 to 7, and 9 for diagnosing Alzheimer's disease.

11. A method according to claim 11, for monitoring the effectiveness of a therapeutic treatment of Alzheimer's disease.

12. A method according to any of claims 4, 5, 7 and 8, for detecting histopathological hallmarks of Alzheimer's disease.